Repeated automatic versus ambulatory blood pressure measurement

Repeated automatic versus ambulatory blood pressure measurement: the effects of age and sex in a normal ageing population

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Objectives To study blood pressure adaptation in relation to age and sex. In a subsample, laboratory blood pressure measurements were compared with ambulatory daytime blood pressure measurements to determine the degree of agreement between the two methods. The night-time blood pressure reduction was analysed as a function of blood pressure status, age and sex.

Design A cross-sectional study in 469 healthy volunteers, aged 23–82 years, stratified for age, sex and educational level.

Methods Laboratory blood pressure was measured automatically (Dinamap 8100) five times during a 20 min recording session. Cardiovascular events in the medical history were identified in order to treat the cardiovascular event-free group separately in subsequent analyses. Within 3 weeks after laboratory blood pressure measurement, ambulatory blood pressure was measured for 24 h in 135 volunteers from the main study.

Results Both diastolic and systolic blood pressure varied markedly in a single measurement session as a function of age, independent of mean pressure level. After 15 min no further blood pressure decrease was observed. On the basis of the average of the final two blood pressure measurements, 18.8% of the subjects were in the hypertensive range (WHO/ISH guidelines). Ambulatory blood pressure measurements were in accord with earlier findings and correlated 0.74 and 0.73 with laboratory diastolic and systolic blood pressure, respectively, but weighted κ values indicated only moderate agreement (0.42 and 0.51). Women showed a more profound reduction in cnight-time blood pressure than did men.

Conclusions There is a substantial change in blood pressure during a single measurement session which is greater in older age groups. The moderate agreement between the two methods of blood pressure measurement supports the notion that blood pressure measured in a single session has limited generalizability to average daytime levels in a population sample.

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Introduction

Hypertension has an important role in the pathogenesis of cardiovascular and cerebrovascular disease. Although it is recognized that repeated blood pressure measurements on separate occasions are necessary to reach a definite diagnosis of hypertension [1], this may not always be feasible in large population-based studies. It is common practice in epidemiological studies to define blood pressure status on the basis of measurements taken during a single visit. This procedure may produce a less accurate estimate of the average habitual blood pressure as a result of uncontrolled environmental conditions, in addition to the normal physiological variability in blood pressure [2]. In particular, the 'alerting reaction' to blood pressure measurement, resulting in a transient pressor response, is a well described clinical phenomenon, which is to a large extent determined by the presence of a medical professional [3,4]. Besides the average blood pressure level, short-term changes in blood pressure and diurnal variation are potential factors that may mediate the detrimental effects of hypertension [5]. The variability of circadian blood pressure is known to increase with age [6] and the extent to which this may interfere with blood pressure adaptation during a measurement session is not clear.

The main focus of this study was to determine age- and sex-related changes in blood pressure measured in a laboratory setting, on the basis of repeated oscillometric measurements during a single session. This was necessary in order to define an optimal estimate of the habitual blood pressure after adaptation. In the next step laboratory blood

pressure values were compared with daytime averages, obtained by 24 h ambulatory blood pressure monitoring, for a subgroup of subjects. Because the extent to which single session blood pressure measurements in a non-clinical population can be generalized to average blood pressure on the basis of repeated measurements over a longer period of time is not clear, we further analysed the agreement between single session blood pressure and average blood pressure during normal daily activities. Finally, the effects of age and sex on the circadian blood pressure rhythm were evaluated.

In this study, which is a part of the Maastricht Ageing Study (MAAS [7]), blood pressure was measured in a healthy population sample aged 23–82 years. The panel was stratified for age and sex, and thus the data allowed the analysis of the effect of these variables on blood pressure and its variability. The rationale for introducing blood pressure into the MAAS study, which is primarily focused on determinants of cognitive ageing, is the increasing evidence that hypertension may have a role in age-related cognitive decline (for a review see [8]). In this respect, there is special interest in ambulatory blood pressure monitoring because the blood pressure measurements obtained with this technique are superior to single blood pressure measurements in predicting latent cerebrovascular disease in elderly subjects [9].

The specific questions addressed in this exploratory study can be summarized as follows: how is age related to the adaptation of blood pressure in a laboratory setting and what are the effects of age, sex and cardiovascular status on diastolic and systolic blood pressure? How is blood pressure measured in the laboratory related to comparable ambulatory measures, and, finally, what effect do chronological age and sex have on the differences in daytime and night-time blood pressure?

Methods

Subjects

A total of 469 community-dwelling subjects were recruited from a register of family practices [10]. Exclusion criteria were previous or current medical conditions with known impact on cognitive function, namely overt cerebrovascular diseases (including strokes), chronic neurological pathology (e.g., dementia, epilepsy and Parkinson's disease), mental retardation, or chronic psychotropic drug use. The sample was stratified for age (12 classes, ranging from 25 ± 1, 30 ± 1, 35 ± 1, ..., 80 ± 1 years; age 51.4 ± 16.8 years, mean $\pm$ SD), sex and two levels of occupational activity, to control for the effect of relevant cognitive performance predictors. For the purpose of data presentation in this study two successive pairs of age groups were combined to form new age classes (25–30, 35–40, ..., 75–80 years). Participants were reimbursed for their travel expenses and received a small gift.

Procedure

All of the 469 subjects completed a postal questionnaire and were visited at home by a research nurse who performed a semistructured medical interview. Detailed information about the medical history and use of medication was obtained during this session. Next, all of the participants were tested within 2 weeks of the home visit in a neuropsychological test laboratory. A broad range of cognitive tests were administered in two test clusters of 1 h each, during a morning (0900–1200 h) or afternoon (1330–1630 h) session. During an intervening 25 min period blood pressure was measured five times in the left arm, with the subject in the seated position, using an oscillometric technique. A Dinamap 8100 (Critikon, Tampa, Florida, USA) monitor with the appropriate cuff size (small, medium, or large adult) was programmed for automatic blood pressure measurement at 5 min intervals. During the measurement interval the subject was left unattended and was instructed to refrain from smoking, to relax and to remain seated until the research assistant returned. A subgroup of 135 subjects in the six age classes 30, 40, 50, 60, 70 and 80 (± 1) years agreed to participate in 24 h ambulatory blood pressure monitoring, scheduled 1–4 weeks later at a convenient time for the subject. The subjects visited the hypertension laboratory of the university hospital between 0800 and 0900 h, where a blood pressure monitor (SpaceLabs 90207; SpaceLabs Inc., Redmond, Washington, USA) was attached to the subject. It was programmed to measure blood pressure four times in 1 h during the day (0700–2259 h) and twice every hour at night (2300–0659 h). All of the subjects were asked to refrain from unusual physical activities and to adhere to their regular sleeping hours.

The prevalence of cardiovascular morbidity was expressed as the presence of one or more of the following disorders or events reported in the medical interview: angina pectoris, cardiac arrhythmia, myocardial infarction, cardiac insufficiency, valvular lesions, heart surgery, peripheral atherosclerosis and cardiac reanimation. A subjective report of hypertension and the use of antihypertensive medication were recorded separately. On the basis of this information the subjects were divided into groups with and without cardiovascular events. The cardiovascular event group was defined by the reported occurrence of current or past cardiovascular disorders or events (excluding hypertension) or the current use of antihypertensive drugs, or both. The subjective report of a diagnosis of hypertension was not considered sufficient unless the subject was also receiving antihypertensive drugs. These medical population characteristics are summarized in Table 1. There was no clinical evidence for renal or renovascular abnormalities in the study group.

All of the subjects were classified into two categories of blood pressure status, on the basis of the average of the fourth and fifth blood pressure measurements, namely

Table 1 Presence of reported hypertension, use of antihypertensive medication and cardiovascular morbidity by age class and sex.

	Age class (years)													
	25–30		35–40		45–50		55–60		65–70		75–80		Row total	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Reported hypertension	4		6	2	12	4	7	12	9	18	5	13	45	49
Antihypertensive drug use	1		1		5	5	7	8	11	14	15	11	40	38
CVE	1	1	1		6	6	9	11	22	16	24	13	63	47
n	41	40	40	41	40	41	40	41	41	40	35	29	237	232

CVE, cardiovascular event group including angina pectoris, cardiac arrhythmia, myocardial infarction, cardiac insufficiency, valvular lesions, heart surgery, peripheral atherosclerosis, reanimation and use of antihypertensive drugs.

normal blood pressure when systolic blood pressure was <140 mmHg and diastolic blood pressure <90 mmHg, and hypertension when systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Isolated systolic hypertension was defined as a systolic blood pressure ≥ 140 mmHg with diastolic pressure remaining below 90 mmHg. These criteria are currently being proposed by the World Health Organization (WHO) for classification of hypertension on the basis of standard office readings on repeated occasions [1].

The ambulatory blood pressure monitoring values were classified using the regression equations that were used to describe the relation between mean laboratory blood pressure and mean daytime ambulatory blood pressure in this study. The WHO/International Society for Hypertension (ISH) cut-off points for normotension (140/90 mmHg) were entered into these equations for systolic and diastolic blood pressure separately to compute the corresponding ambulatory blood pressure monitoring values; daytime mean blood pressure above 135.2/88.6 mmHg was considered to be in the hypertensive range. We used this procedure because no definite reference values for ambulatory blood pressure monitoring are yet available for clinical purposes.

Statistical analysis

Diastolic and systolic blood pressure were treated separately in all subsequent analyses. Linear and non-linear effects of age on blood pressure change within 20 min were tested in a one-way analysis of variance procedure. For this analysis the difference between blood pressure at the first and last measurement was expressed as the absolute difference and as a percentage of the average blood pressure over five measurements. This average was corrected for the effect of mean absolute blood pressure level on blood pressure variability [6], using the formula

$$(M_1 - M_5) \times 100 / [(M_1 + M_2 + M_3 + M_4 + M_5)/5]$$

where M_1 indicates the blood pressure at the time of first measurement and so forth. The end of blood pressure adaptation was defined as the absence of a significant decrease in systolic and diastolic blood pressure between two consecutive measurements, using paired Student's *t*-tests with an adjusted $P = 0.01$ (Bonferroni correction for multiple comparisons). Multiple hierarchical regression analysis was used to test the effects of the independent variables cardiovascular event group membership, age, sex and the age × sex interaction term on laboratory blood pressure outcome, and to evaluate the effect of blood pressure status, age, sex and age × sex interaction on day–night blood pressure differences, in terms of the overall proportion of variance explained in the outcome measure. In the case of a significant contribution of a variable to the explained overall variance, its associated partial regression coefficient (B) and the 95% confidence interval were presented. Comparisons between estimates of mean and variability in blood pressure based on laboratory measurement or ambulatory blood pressure monitoring were presented as Pearson's r and as weighted κ (K_w). K_w is commonly used as a measure of agreement (concordance) because it expresses the degree of interchangeability between two measurements that are intended to assess the same concept, whereas r is only an index of general relatedness, or 'trend' [11]. For this purpose all ambulatory daytime parameters were ranked in quartiles. Next, laboratory parameters were ranked according to the same ambulatory daytime classification criteria. From the resulting 4 × 4 cross-tabulation table, K_w was computed.

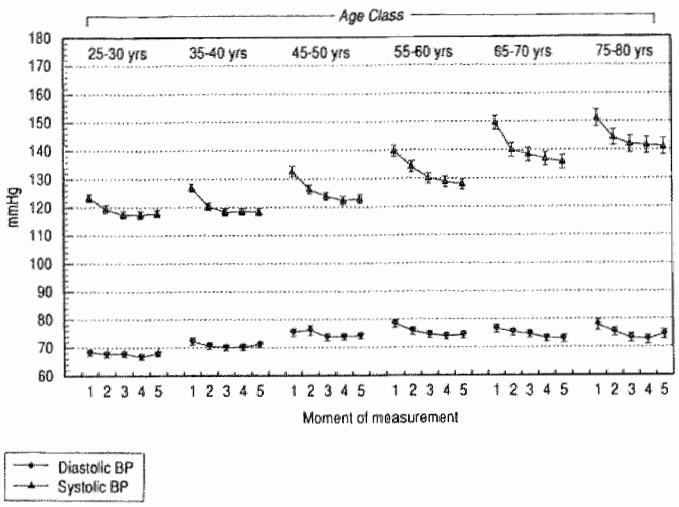
Deviation from normality of day–night blood pressure differences was tested using the Kolmogorov–Smirnov test statistic. $P < 0.05$ was considered statistically significant. All analyses were performed with the SPSS program series [12].

Results

Relation between age and blood pressure adaptation during repeated laboratory measurement

The average systolic and diastolic blood pressures during the laboratory session were calculated for every consecutive measurement (M) and age class (Fig. 1). A steady overall increase in systolic blood pressure was observed with age. The increase in diastolic blood pressure was less extreme and diastolic blood pressure remained relatively constant after 45–50 years of age. Furthermore, a gradual mean decrease in systolic and (again less extreme) diastolic blood pressures over consecutive measurements was apparent.

Fig. 1.



Mean systolic and diastolic blood pressures (BP) on five consecutive measurements within 20 min. Separate plots are shown for different age classes. Error bars indicate the standard error of the mean; total group, n=469.

A linear increase in diastolic and systolic blood pressure difference with age was found, both for the absolute blood pressure differences and for the differences in terms of percentage (one-way analysis of variance, $F(1,456) = 14.8$ and 15.2 (both $P < 0.001$), respectively, for diastolic blood pressure; $F(1,456) = 26.4$ and 16.0 (both $P < 0.001$), respectively, for systolic blood pressure). The mean absolute difference between the first and the last diastolic blood pressure measurements ranged from 0 in the youngest to 5 mmHg in the oldest group. For systolic blood pressure these values were 6 and 12 mmHg, respectively. The same pattern was observed when the subjects of the cardiovascular event group were excluded from the analysis. No evidence was found for a significant non-linear trend in pressure differences with age. Thus, the decrease in diastolic and systolic blood pressure during the measurement interval was more profound with increasing age, even after correction for the mean pressure level.

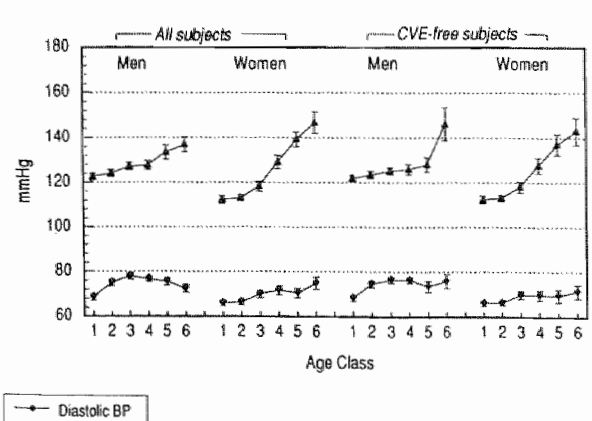
In the next step it was determined when this decrease in blood pressure was completed. Differences in blood pressure of four successive pairs of measurements (1 − 2, 2 − 3, 3 − 4 and 4 − 5, respectively) computed for the total group were 1.3 ($t = 2.9$, $P < 0.01$), 1.1 ($t = 3.0$, $P < 0.01$), 0.7 ($t = 2.6$, $P < 0.05$), and − 0.7 mmHg ($t = -2.3$, NS) for diastolic, and 6.5 ($t = 15.0$, $P < 0.001$), 2.4 ($t = 5.9$, $P < 0.001$), 1.0 ($t = 3.0$, $P < 0.01$), and 0.3 mmHg ($t = 0.8$, NS) for systolic blood pressure (all analyses df = 461). This indicates that, at least on a group level, no major adaptation of blood pressure is to be expected after measurement 4. On the basis of these results we chose to average the diastolic and systolic blood pressure levels of measurement 4 and 5 as the optimal estimates of habitual blood pressure after adaptation. These averages were used in further analyses.

Effects of age, sex and cardiovascular status on adapted diastolic and systolic blood pressures

Figure 2 illustrates the relation between age class and diastolic or systolic blood pressure, for male and female participants separately. Additional plots are shown for the group with no reported cardiovascular events in their medical history.

The effects of membership of the 'cardiovascular event' group, calendar age, sex and age × sex interaction on diastolic and systolic blood pressures were analysed in two hierarchical multiple regression analyses. In both regression models, cardiovascular event membership (0 = no, 1 = yes) was entered in the first step and sex (1 = male, 2 = female), age × sex interaction and calendar age in the second step. The overall proportion of the variance explained in the final models by these variables was 0.09 and 0.27, for diastolic and systolic blood pressure respectively, both at the $P < 0.001$ level. The presence of cardiovascular events was associated with higher diastolic (partial regression coefficient B = 2.7, 95% confidence interval for B = 0.2–5.3; $P < 0.05$) and systolic blood pressure (B = 5.3, 95% confidence interval = 1.5–9.2; $P < 0.01$). Women showed lower mean diastolic blood pressure levels (B = − 4.6, 95% confidence interval = − 6.5 to − 2.7; $P < 0.001$) but the same trend in systolic blood pressure was not significant. Only in systolic blood pressure was a substantial age × sex interaction found (B = 3.7, 95% confidence interval 2.3–5.1; $P < 0.001$), indicating a more prominent increase in mean systolic blood pressure with age in women than in men (Fig. 2). Calendar age was associated with higher diastolic (B = 0.1,

Fig. 2.



Average laboratory systolic and diastolic blood pressures (BP), by age class (1, 25–30 years to 6, 75–80 years) and sex, for the total group (n = 469) and for the group free of cardiovascular events, n = 349), separately. Error bars indicate the standard error of the mean.

Table 2 **Hypertensive status in terms of percentage (WHO/ISH criteria) and prevalence of isolated systolic hypertension in different subgroups.**

	n	Age class (years)						All ages
		25–30	35–40	45–50	55–60	65–70	75–80	
Hypertension								
Men	237	4.9	17.5	15.0	15.0	26.8	40.8	19.4
Women	232	0.0	0.0	7.3	22.0	42.5	44.8	18.1
All	469	2.5	8.6	11.1	18.5	34.6	42.2	18.8
CVE-free group	359	1.3	7.5	10.1	16.4	20.9	48.1	12.8
Isolated systolic hypertension								
Men	237	2.4	7.5	5.0	12.5	19.5	34.3	13.1
Women	232	0.0	0.0	7.3	14.6	32.5	31.0	13.4
All	469	1.2	3.7	6.2	13.6	25.9	32.8	13.2
CVE-free group	359	0.0	3.8	7.2	13.1	14.0	40.7	9.2

CVE, cardiovascular event.

95% confidence interval 0.0–0.1; $P < 0.05$) and systolic blood pressure (B = 0.4, 95% confidence interval 0.3–0.5; $P < 0.001$).

Table 2 summarizes the hypertensive status for each age class, on the basis of the WHO/ISH classification criteria. The prevalence of hypertension gradually increased with age (both uncorrected and corrected for cardiovascular event status) but was lower in the cardiovascular event-free group, except for the subjects aged 75–80 years (48.1 versus 42.2%). The proportional contribution of isolated systolic hypertension rose with age, from 0.48 and 0.00 in the 25–30 year group, to 0.78 and 0.85 in the 75–80 group, for the cardiovascular event uncorrected and corrected groups, respectively.

Laboratory blood pressure and its variability in relation to ambulatory blood pressure

Of 135 subjects who participated in the additional 24 h blood pressure measurements within 4 weeks of the laboratory tests, 28 reported one or more cardiovascular events in their medical history, or were using antihypertensive medication. In addition, eight ambulatory recordings yielded incomplete data during the night-time period because some subjects felt uncomfortable wearing the cuff during sleeping hours, leaving 99 subjects for the 24 h ambulatory blood pressure data presented in Table 3. No subjects reported unusual sleeping episodes or abnormal events during the night.

Several aspects of laboratory and ambulatory daytime measurements were analysed for all 135 subjects. The averages of the laboratory diastolic and systolic blood pressures at measurements 4 and 5 were used as the mean habitual blood pressure. The standard deviation of five repeated measurements and differences in diastolic and systolic blood pressures at measurements 1 and 5 were analysed as estimates of pressure variability. These parameters of laboratory blood pressure were compared with the mean diastolic and systolic ambulatory daytime blood pressure. Variability in ambulatory daytime blood pressure was defined as the difference between the highest and the lowest diastolic or systolic daytime blood pressure and as the daytime standard deviation of these pressures. Correlations (Pearson's r) were computed between continuous scaled laboratory and ambulant parameters as indices of general relatedness. In addition, weighted κ (K_w) was used to test the agreement (concordance) between these measures. Analyses were performed separately for the total group and for the 'cardiovascular event-free' group (Table 4). For both groups there was a moderate correlation and concordance for mean blood pressure parameters but low correlations and extremely poor concordance for estimates of variability.

The relation between ambulatory daytime blood pressure and laboratory blood pressure was studied in more detail. Using the scatterplots for diastolic and systolic blood pressures presented in Figure 3, we determined regression equations that predicted daytime blood pressure from laboratory measurements in all of the subjects. These were $40.9 + 0.53x$ ($r = 0.74$, $P < 0.01$) and $59.6 + 0.54x$ ($r = 0.73$, $P < 0.01$) for diastolic and systolic blood pressures, respectively. Laboratory measurement clearly underestimates mean daytime blood pressures in the lower pressure range but overestimates in the high-pressure range (the regression line and 'line of identity' intersect at 130 and 87 mmHg for systolic and diastolic blood pressure, respectively). This is even clearer when the differences between laboratory and ambulatory daytime means for diastolic and systolic blood pressures are plotted against their means (Fig. 4). This method is commonly used to compare two clinical assessments when systematic measurement bias is suspected [13]. Diastolic blood pressure measured in the laboratory tended to be systematically lower than ambulatory daytime diastolic pressure, but the difference became smaller and eventually disappeared with higher levels of diastolic blood pressure. In approximately 95% of the present subjects, the difference ranged between 6.9 and − 21.6 mmHg. The difference in systolic pressures tended to change from a negative to a positive

Table 3 The 24 h ambulatory blood pressure for each age class and sex. Only subjects with no cardiovascular events in their medical history and with complete 24 h pressure readings are included (n = 99).

	Age class (years)						Sex		
	30	40	50	60	70	80	M	F	All
Total n	16	18	25	18	14	8	55	44	99
M/F	10/6	7/11	14/11	11/7	7/7	6/2			
Laboratory mean blood pressure (mmHg)									
Systolic	121 ± 11	116 ± 11	124 ± 14	125 ± 11	134 ± 11	135 ± 23	129 ± 13	119 ± 14	125 ± 14
Diastolic	70 ± 7	70 ± 11	75 ± 12	76 ± 8	69 ± 12	70 ± 13	76 ± 10	67 ± 10	72 ± 11
Ambulatory daytime mean blood pressure (mmHg)									
Systolic	124 ± 9	123 ± 10	127 ± 9	125 ± 9	130 ± 14	133 ± 16	129 ± 10	124 ± 11	126 ± 11
Diastolic	76 ± 5	79 ± 9	83 ± 7	80 ± 7	78 ± 8	77 ± 10	81 ± 8	77 ± 8	79 ± 8
Ambulatory night-time mean blood pressure (mmHg)									
Systolic	110 ± 8	107 ± 10	113 ± 11	111 ± 10	116 ± 15	120 ± 20	115 ± 11	109 ± 13	112 ± 12
Diastolic	61 ± 4	64 ± 10	69 ± 8	67 ± 9	63 ± 10	64 ± 12	68 ± 9	62 ± 8	65 ± 9
Ambulatory 24 h means blood pressure (mmHg)									
Systolic	121 ± 9	120 ± 11	124 ± 9	121 ± 9	127 ± 14	130 ± 17	126 ± 10	120 ± 11	123 ± 11
Diastolic	72 ± 5	76 ± 9	80 ± 7	77 ± 7	75 ± 8	73 ± 10	78 ± 8	74 ± 7	76 ± 8

Values are expressed as means ± SD. M, male; F, female.

value with increasing mean pressure. Furthermore, a slight increase in variability was observed with increasing mean pressure, suggesting an increase in error bias. For systolic blood pressure the 95% limits of agreement ranged from −22.1 to 19.3.

In order to put the relationship between the two methods of measurement in a more clinical perspective, we classified the blood pressure status of all ambulatory blood pressure monitoring participants on the basis both of their laboratory value (using the WHO/ISH criteria) and of their mean daytime blood pressure, according to the predicted ambulatory blood pressure monitoring values (135.2/88.6 mmHg) that were calculated by entering the WHO/ISH cut-off points (140/90 mmHg) into the regression equations presented above. A total of 19 out of 39 subjects in the ambulatory blood pressure monitoring group, who were classified as hypertensive on the basis either of ambulatory or of laboratory measurement, were classified as hypertensive using both methods, four subjects were in the hypertensive range in the laboratory only and 16 subjects were hypertensive on the basis of ambulatory blood pressure monitoring values only. These results indicate that the agreement between the two methods is poor when clinical criteria for grouping are used.

Table 4 Relationship between mean blood pressure and estimates of variability [difference between highest and lowest recording (DHL) and the standard deviation (SD)] of laboratory and ambulatory daytime blood pressure measurement.

	Total group (n = 135)		'Cardiovascular event-free' group (n = 106)	
	r	K_w	r	K_w
Diastolic blood pressure	0.74**	0.42	0.74**	0.56
Mean arterial pressure	0.71**	0.49	0.69**	0.55
Systolic blood pressure	0.73**	0.51	0.73**	0.56
DHL diastolic	0.13	0.00	0.10	0.00
DHL mean arterial	0.23**	0.01	0.17	0.07
DHL systolic	0.23**	0.02	0.25**	0.00
SD diastolic	0.24**	0.06	0.21*	0.07
SD mean arterial	0.36**	0.15	0.24*	0.13
SD systolic	0.28**	0.11	0.32**	0.08

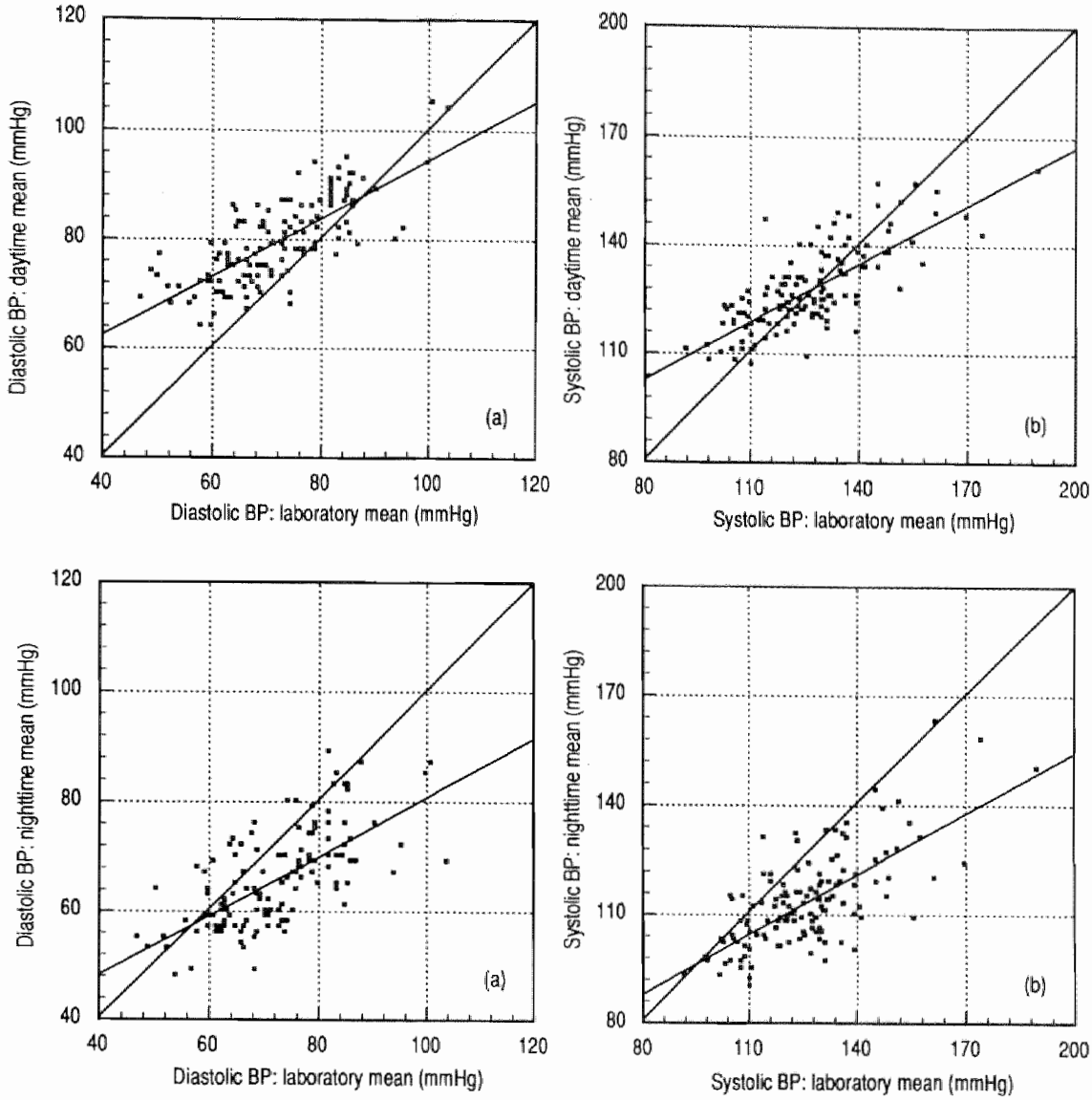
The relationship is expressed in terms of correlation (Pearson's r) and agreement (weighted κ, K_w), the latter based on classification of ambulatory daytime values in quartiles. The total group and cardiovascular event-free group are described separately.
Strength of agreement is measured by K_w: < 0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; > 0.80, very good [28]. *$P < 0.05$. **$P < 0.01$.

Age- and sex-related effects on daytime and night-time blood pressure differences

Ninety-nine antihypertensive drug-free subjects with no cardiovascular event in their medical history were included in the analysis. Twelve subjects in this group could be classified as 'non-dippers', showing overall night-time reductions in systolic and diastolic blood pressure of less than 10% compared with daytime values [14]. Day–night differences in diastolic and systolic blood pressure were normally distributed; tests to detect deviation from normality (Kolmogorov–Smirnov) were not significant for the distribution of both pressure differences [0.04 and 0.07 (df = 99), for diastolic and systolic blood pressure, respectively]. This clearly demonstrates that the night-time reduction in blood pressure ('dipping') is a gradual phenomenon that follows a unimodal distribution. Therefore, any classification rule for 'dipper' status may be considered largely arbitrary.

Finally, the extent to which day–night differences in blood pressure could be explained by the factors hypertensive status, age, sex and the age × sex interaction term, was

Fig. 3.



Scatter plots of diastolic and systolic blood pressures measured in the test laboratory and with daytime ambulatory recording (upper plots, total group n = 135) and night-time ambulatory recording (lower plots, total group n = 127). The 'line of identity' and regression line are also displayed.

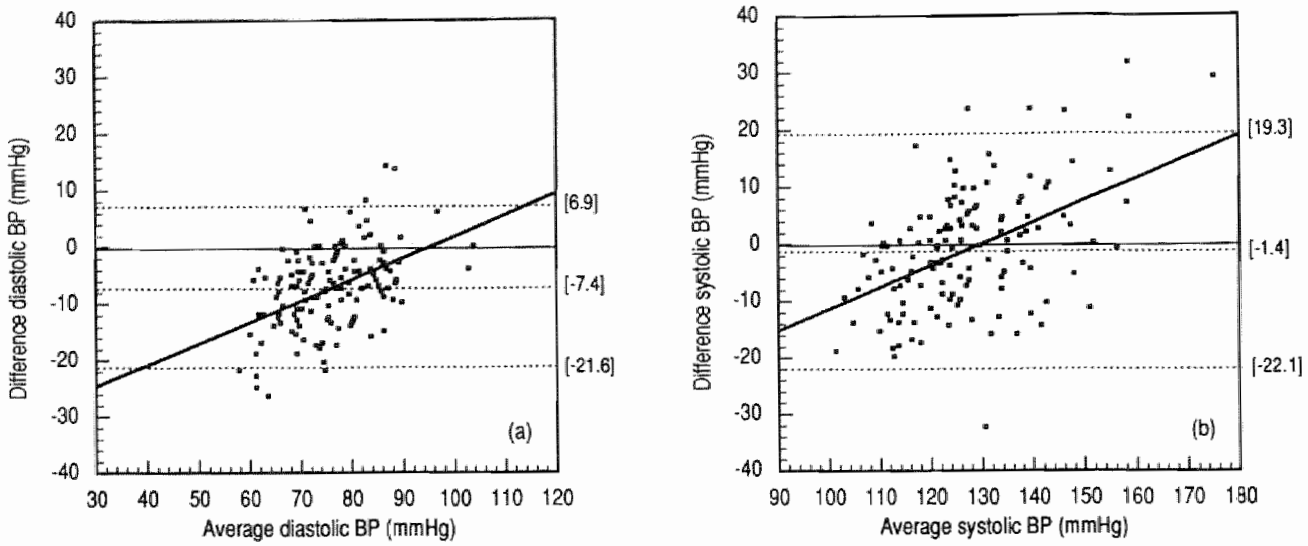
analysed in two separate hierarchical multiple regression models for diastolic and systolic blood pressure. Hypertensive status, on the basis of daytime average blood pressure and predicted WHO/ISH cut-off points, was entered as the first variable in the model; all other variables were entered in step 2. Day–night blood pressure differences were not influenced by hypertensive status, age or the age × sex interaction term. Only sex contributed significantly to explained variance in diastolic day–night blood pressure difference; the night-time decrease in diastolic blood pressure was predicted to be 3.0 mmHg greater for women than for men when all other variables were controlled for (B = 3.0, 95% confidence interval 0.9–5.0; $P < 0.01$). The final models predicted 12 ($P < 0.05$) and 2% (not significant) of the variance in day–night differences of diastolic and systolic blood pressure, respectively.

Discussion

Blood pressure adaptation and age

One of the main features of our study is that the reduction in systolic and diastolic blood pressure, measured automatically over a 20 min period, increased with age. This effect was still present when blood pressure differences over time were corrected for mean blood pressure levels. Using a different approach, Mancia *et al.* [3] found no direct relation between age and adaptation to an intra-arterial measured blood pressure response that was induced by the presence of a medical professional.

Fig. 4.



Bland–Altman plots for diastolic and systolic blood pressures (BP); differences in pressure (laboratory minus mean daytime values) are plotted against the average of the two measures. Thin dotted lines indicate the mean difference and the distance of 2SD from the mean; 95% of cases tend to fall within these limits ('95% limits of agreement'); skewed lines indicate regression lines.

However, they studied a smaller (n = 46) and younger group (age range 16–64 years) of hospitalized inpatients of mixed hypertensive status in a less standardized measurement environment. It can even be argued that the observed effects of age on blood pressure adaptation will be even greater in a clinical setting, in particular in hypertensive patients. For instance, all our measurements were performed in the absence of an observer, thereby minimizing a possible pressor response (the 'white coat' effect [15]) and measurement bias. Furthermore, the pressure response in our experimental setting may be less extreme because the individuals were less stressed, because the blood pressure measurement had no direct implications for medical intervention [4]. Finally, blood pressure variability is greater in hypertensive subjects [16]. Until these studies are repeated in a clinical setting it seems reasonable not to underestimate the effect of age on blood pressure adaptation during a measurement session.

We conclude from trend analysis of five consecutive measurements in 20 min that adaptation of blood pressure took place within 10–15 min on average, and, furthermore, that the blood pressure measured after this episode reflects the basal blood pressure more accurately than does the average of all five measurements taken together. Although risk estimates for blood pressure in the pathogenesis of vascular disease are based on unavoidably biased casual measurements in a doctor's office, we adhere to the use of an approximated 'basal' blood pressure because there is evidence that blood-pressure-mediated target organ damage is more closely related to 24 h ambulatory blood pressure than to office values [17,18]. We chose to use an adaptation period of 15 min before basal blood pressure recordings were made. Fifteen minutes of adaptation is in any case longer than the 'several minutes' advised by the WHO/ISH guidelines for office blood pressure measurement [1]. However, some authors [19,20] have shown that increasing the number of blood pressure measurements by using (semi-) automatic devices may enhance the reproducibility of blood pressure estimates, expressed as the reciprocal of the standard deviation of the differences between measurements (1/SD). Although these observations were made in hypertensive subjects in whom (as mentioned above) blood pressure variability is known to be higher (in contrast to our largely normotensive population) it cannot be excluded that prolongation of the laboratory measurement interval or increasing the number of measurements after 15 min might have improved the prediction of daytime blood pressure in this study.

Blood pressure status and age

Laboratory blood pressure measurements showed a general increase in systolic and diastolic blood pressure with age, the former increase being more extreme in women than in men. These results are in accord with earlier findings of large population studies in which classical sphygmomanometric measurements were made (e.g. the National Health and Nutrition Examination Survey 1976–1980 (NHANES II) [21]). The same patterns for age and sex were found in the prevalence of hypertension when criteria proposed for office blood pressure readings were used. However, it must be taken into account, that the prevalence of hypertension in this study may be slightly

underestimated by the generally lower blood pressure values obtained by automatic measurement compared with office readings. In contrast, the fact that blood pressure was measured on only one occasion may have produced the opposite effect, because in clinical settings blood pressure tends to decrease on repeated visits. The percentage of men with blood pressure in the hypertensive range gradually increased from 4.9% in the group aged 25–30 years to 40.8% in the group aged 75–80 years. Women with hypertension were first found in the group aged 45–50 years (7.3%), after which the percentage rose steeply towards 44.8% in the 75–80 year group. Even in the cardiovascular event-free group, the prevalence of untreated hypertension was substantial (12.8%). However, hypertension was less prevalent in the cardiovascular event-free subjects in all age groups, except for those aged 75–80 years, for whom the opposite was true. It is not clear whether this indicates a selective undertreatment in this group. The prevalence of isolated systolic hypertension in our population is in accord with earlier findings that isolated systolic hypertension is largely restricted to the older age groups [22].

Comparison between parameters of laboratory and ambulatory blood pressure measurement

The mean values for 24 h ambulatory blood pressure measurements were similar to earlier published reference data [23,24]. Daytime and night-time values for women were slightly higher in this study than the values reported by O'Brien *et al.* [23] (124/77 daytime and 109/62 mmHg night-time in our study, versus 118/75 and 102/58 mmHg in their study).

The blood pressure measured in the doctor's office is systematically higher than values derived from ambulatory measurements [23]. Our laboratory diastolic blood pressure levels were lower than the ambulatory daytime values, whereas systolic blood pressures did not differ (7.2 mmHg, $P < 0.001$, versus 1.2 mmHg, NS, respectively). We expect this to be, at least partly, a result of a lower pressor response (or 'white coat' effect) in our study.

Correlations between laboratory and ambulatory daytime blood pressure values for systolic and diastolic blood pressure measurements were 0.73 and 0.74, respectively, and are comparable to those of other studies. Enström [25] found correlations of 0.81 systolic and 0.61 diastolic between ambulatory daytime blood pressure and blood pressure measured repeatedly in a doctor's office in a group of 48 middle-aged normotensive men, and lower correlations between the same measures in 81 borderline hypertensive middle-aged men (0.62 and 0.54 for systolic and diastolic blood pressure, respectively). Staessen *et al.* [24] found correlations of 0.72 and 0.60 for systolic and diastolic blood pressures between blood pressure measured repeatedly by a trained observer at home and mean ambulatory daytime blood pressure, in a population sample aged 20–81 years (n = 328). Correlations between measures of variability in this study were significant, but low. However, the extremely poor agreement between the measures of variability indicates that the blood pressure variability of repeated measurements on a single occasion is not comparable in magnitude to the spontaneous fluctuation of ambulatory daytime blood pressure. This is not surprising because the circumstances under which variability was assessed were essentially different for the two measurements. The laboratory indicators of variance (SD and highest and lowest blood pressure difference) are more related to standardized blood pressure adaptation with the subject in a resting position, whereas SD in ambulatory daytime recordings is more determined by less controllable environmental factors such as physical activity or posture.

Notwithstanding the reasonable correlations between daytime mean and laboratory pressures, the difference between the two pressures varied with the average diastolic and systolic blood pressure level in an almost linear fashion. The systematic discrepancies between the two measurement procedures are reflected in only moderate weighted κ values when the values measured using the two methods for systolic, mean arterial and diastolic blood pressure are classified uniformly. In addition, classification of hypertensive status may lead to different results depending on the chosen type of measurement. If the laboratory blood pressure measurements were to be used to predict ambulatory daytime values a linear transformation of the data would seem to be appropriate. However, the fit of such a model may be rendered poor by an increase in error bias with increasing mean blood pressure level, as can be observed for systolic blood pressure in Figure 4b. One has to bear in mind therefore that estimation of habitual daytime blood pressure from laboratory blood pressure levels during a single session is more error-prone with increasing blood pressure level.

Another factor that may have attenuated the accuracy of prediction in ambulatory blood pressure values is that the time of the laboratory session within the day was not fixed. Di Rienzo *et al.* [26] have shown that difference between mean 24 h blood pressure and subsequent 30 min intervals of such recordings shows considerable diurnal variation. It can be argued that fixed daytime measurement intervals will reduce this type of inaccuracy.

Day–night blood pressure difference

The sex of the subject was the only factor that contributed significantly to the variance in day–night diastolic blood pressure difference, with women tending to have a larger blood pressure difference than had men. Age and hypertensive status did not have a significant effect. The commonly used classification according to dipper' status

[14] may suggest a bimodal distribution of blood pressure level difference, where a sharp distinction can be made between 'dippers' and 'non-dippers' according to a dichotomous criterion. Our data clearly demonstrate the continuous, normal distribution of day–night blood pressure differences and that any classification for 'dipper status' is essentially arbitrary in this largely normotensive population sample. It needs to be confirmed in future research whether the day–night difference in blood pressure shows a normal distribution in hypertensive groups also, but at this point we prefer to include the absolute decrease in day–night blood pressure instead of dipper status in any risk analysis that pertains to the relationship between day–night blood pressure differences and target organ damage.

Conclusion

In summary, these findings demonstrate that the importance of an adequate adaptation phase for single blood pressure measurement increases with age. We chose to average blood pressure measurements after 15 and 20 min of relaxation because no further decrease in blood pressure was observed after 15 min on a group level. Furthermore, it was confirmed that, at least for daytime ambulatory blood pressure, a clear linear relation with laboratory blood pressure can be demonstrated in a (largely) normotensive population sample. However, defining the hypertensive status on the basis of either of the two measurements separately may lead to unequivocal conclusions, because the error bias in predicting ambulatory systolic blood pressure from laboratory measurements of systolic blood pressure is likely to increase as the absolute pressure level increases. As stated earlier, parameters of ambulatory blood pressure may reflect the blood pressure load that leads to target organ damage more accurately than do pressure levels derived from single measurements alone. Current knowledge about the relationship between blood pressure and target organ disease is largely based on studies in which casual (repeated) blood pressure measurements were made and there is still much debate concerning the use of parameters related to ambulatory blood pressure as more sophisticated risk factors for vascular morbidity and mortality [27]. We therefore suggest that vascular risk estimates based on ambulatory blood pressure and repeated single measurements should be treated as different entities until the relation between blood pressure, measured with combined techniques, and vascular damage has been elucidated further.

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